PTO/SB/22 (06-04)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) CIBT-P01-099
Application Number 09/844257	Filed April 27, 2001
For METHODS AND REAGENTS FOR TISSUE ENGINEERING OF CARTILAGE IN VITRO	
Art Unit 1646	Examiner M. T. Brannock

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
[ ]	One month (37 CFR 1.17(a)(1))	$110.00	$55.00	$
[x]	Two months (37 CFR 1.17(a)(2))	$430.00	$215.00	$ 430.00
[ ]	Three months (37 CFR 1.17(a)(3))	$980.00	$490.00	$
[ ]	Four months (37 CFR 1.17(a)(4))	$1,530.00	$765.00	$
[ ]	Five months (37 CFR 1.17(a)(5))	$2,080.00	$1,040.00	$

[ ] Applicant claims small entity status. See 37 CFR 1.27.

[ ] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[x] The Director has already been authorized to charge fees in this application to a Deposit Account.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 18-1945 . I have enclosed a duplicate copy of this sheet.

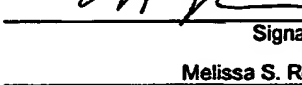
I am the

[ ] applicant/inventor.

[ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

[x] attorney or agent of record. Registration Number 54,408

[ ] attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) _____



Signature — November 5, 2004 (Date)

Melissa S. Rones, Ph.D. (Typed or printed name) — (617) 951-7653 (Telephone Number)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

[x] Total of 1 forms are submitted.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 11/5/04 Signature: _____ (Ginny Blundell)

DEP'T REF 807

Docket No.: CIBT-P01-099

2005 MAR -7 PM 4:29 (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kellner et al.

Application No.: 09/844257

Confirmation No.: 8923

Filed: April 27, 2001

Art Unit: 1646

For: METHODS AND REAGENTS FOR TISSUE ENGINEERING OF CARTILAGE IN VITRO

Examiner: M. T. Brannock

REQUEST FOR REFUND

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby request a **$430.00** credit to our Deposit Account 18-1945. Evidence of our request for credit is detailed below.

On May 5, 2004 a final office action was issued with an initial response date of August 5, 2004. A reply was filed on July 27, 2004.

On September 20, 2004 an Advisory Action (attached as Exhibit A) was issued which stated the period for reply expires 4 months from the mailing date of the final rejection (due September 5, 2004).

On October 5, 2004 Applicant filed a Reply to Office Action and a one month extension of time. On October 8, 2004 our Deposit Account was charged the one month extension fee of $110.00. A copy of the Fee Transmittal specifically itemizing the fee is attached as Exhibit B.

On October 14, 2004 our Deposit Account was additionally charged a two month extension of time fee of $320.00. In view of the above, Applicant believes the two month extension fee is incorrect due to the response filed on July 27, 2004 and a credit to our Deposit account of $320.00 is requested.

Additionally, on November 5, 2004 Applicant filed a Notice of Appeal and a request for a two month extension of time. On November 10, 2004 our Deposit Account was charged the Notice of Appeal fee of $340.00 and the two month extension of time fee of $430.00. A copy of the Fee Transmittal specifically itemizing these two fees is attached as Exhibit C.

Applicant erroneously authorized the two month extension of time fee of $430.00 on November 5, 2004. Applicant should have only authorized $320.00 (the 2 month extension of time fee of $430.00 on November 5, 2004 minus the one month extension fee of $110.00 paid on October 5, 2004). Therefore, a credit of $110.00 is requested to our Deposit Account.

Applicant respectfully requests the total credit of **$430.00** to our Deposit Account No. 18-1945.

A copy of this letter is enclosed for accounting purposes.

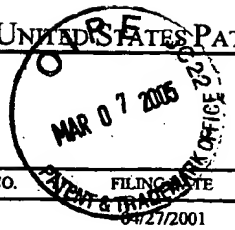
Dated: March 4, 2005

Respectfully submitted,

By _____

Melissa S. Rones, Ph.D.
Registration No.: 54,408
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE



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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,257	04/27/2001	Karin Kellner	CIBT-P01-099	8923

28120 7590 09/20/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

Ropes & Gray

SEP 22 2004

Intellectual Property Dept.

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

REVIEWED BY
DOCKETING

Advisory Action

Application No.	Applicant(s)	
09/844,257	KELLNER ET AL.	
Examiner	**Art Unit**	
Michael Brannock	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: *See attachment*.
3. ☒ Applicant's reply has overcome the following rejection(s): see attachment.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attachment*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-8*.

   Claim(s) withdrawn from consideration: _____.
8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.
10. ☒ Other: *PTO-892*

Attachment to Advisory Action

Applicant is notified that the amendment will not be entered because it raises new issues with regard to 35 USC 103. Specifically, it appears that claims 1-3 and 8 would be rejected under 35 USC 103 as being obvious over Ingham et al, U.S. Patent No: 584409, as set forth previously, in view of either Pepinsky et al. U.S. Patent No: 6444793 or Seytter-T et al., Abstract Number A151, page S536, JBMR ,November 1998, each of whom teach that the use of palmitoylated hedgehog protein is desirable.

Had the amendment been entered, claims 1-2 and 8 would remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5844079 to Ingham et al. because it is an inherent feature of the expression of hedgehog protein in eukaryotic cells (as taught by Ingham, see col 42 for example), that the protein is modified with one palmitoyl moiety, as was well appreciated at the time the instant application was filed, see Seytter-T et al., Abstract Number A151, page S536, JBMR, November 1998. Applicant's arguments have been fully considered but not deemed persuasive, for the reason set forth above, because the examiner maintains that Ingham adequately suggest the particular concentrations of the hedgehog protein, such that one of ordinary skill in the art would arrive at the claimed concentrations as a matter of simple routine optimization of operating parameters for the reasons set forth previously. Applicant does not appear to provide specific reasons as to why this might not be so.

Applicant's proposed amendments and persuasive arguments would have obviated the remaining grounds of rejections had the amendments been entered.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D., can be reached at (571) 272-0961.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

ELIZABETH KEMMERER
PRIMARY EXAMINER

September 8, 2004

Notice of References Cited	Application/Control No. 09/844,257	Applicant(s)/Patent Under Reexamination KELLNER ET AL.	
	Examiner Michael Brannock	Art Unit 1646	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
X	A	US-6,444,793	09-2002	Pepinsky et al.	530/402
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

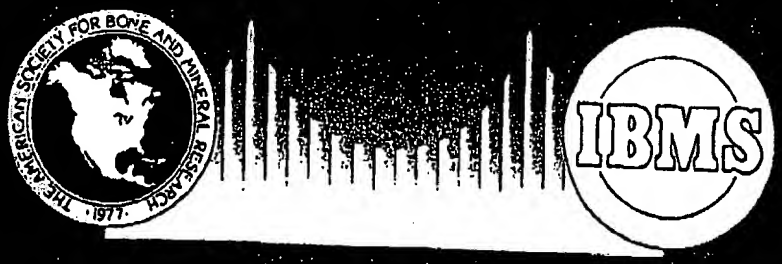
*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Seytter-T et al., Abstract Number A151, page S563, JBMR ,November 1998
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Volume 23, Number 5 (Supplement) November 1998

BONE

Official Journal of the International Bone and Mineral Society



1998 PROGRAM & ABSTRACTS

Second Joint Meeting of
The American Society for Bone and Mineral Research *and* The International Bone and Mineral Society

Moscone Convention Center
San Francisco, California, USA
December 1–6, 1998

This supplement was published in cooperation with

JBMR
Journal of Bone and Mineral Research
The Official Journal of the American Society for Bone and Mineral Research

ELSEVIER

nuclear extracts from keratinocytes grown in 0.03 or 1.2mM calcium, we have determined that the levels of multiple members of the jun and fos family are increased in the nuclei of cells grown in the higher calcium medium. We conclude that calcium induces AP1 proteins in keratinocytes, and the elevated AP1 proteins increase the transcription of involucrin and other genes important for the differentiation process.

SA148

Na^+/Ca^{2+} exchange system is involved in colony stimulating factor-1-induced signal transduction in osteoclast. Hitoshi Amano,[1] Keiko Suzuki,[1] Taro Tsurukai,[2] Shoji Yamada,[1] [1]Pharmacology, Showa University, Tokyo, Japan, [2]Biochemistry, Showa University.

Colony stimulating factor-1 (CSF-1) is essential for formation, differentiation and activation of osteoclast. We have reported that

CSF-1 induced the rise in intracellular Ca^{2+} through the activation of Na^+/H^+ exchanger and Na^+/Ca^{2+} exchanger(NCX). Na^+/Ca^{2+} exchanger catalyzes the electrogenic exchange of 3 Na^+ for 1 Ca^{2+} across the plasma membrane and regulates the intracellular Ca^{2+} levels in many cells. In addition, the NCX is thought to be involved in the bone resorption in both basal and stimulated by PTH. KB-R7943, a new specific NCX1 inhibitor, blocked the outward Na^+/Ca^{2+} exchange current more potently than the corresponding inward current, in contrast to dichlorobenzamil(DCB). In the present study, we sought to confirm the presence of NCX in osteoclasts and to determine the role of its activity in CSF-1-induced signal transduction in osteoclast. Osteoclast formation was studied in 7-day co-cultures of mouse bone marrow cells and primary osteoblasts in the presence of 1,25 $(OH)_2$ vitamin D_3 and PGE_2. To investigate the effect of CSF-1 on the differentiation, mature rat osteoclasts isolated from tibiae and femora of 1-day-old rats were incubated in the presence of 500 pM CSF-1 for 48 hrs with or without 10^{-9} - 10^{-5} M KB-R7943. Treatment with KB-R7943 blocked NCX1 activity, the osteoclastogenesis, F-actin ring formation and bone resorption induced by CSF-1 completely. In addition, NCX1 antisense oligodeoxynucleotide (ODN) reduced the number of tartrate-resistant acid phosphatase-positive multinucleated cells but non-sense or mismatched ODN did not. NCX1 was detected by Western blot analysis and immunocytochemical study with anti-NCX1 antibody. NCX1 was expressed more strongly in the membrane fraction of purified osteoclast than in that of osteoblast. Treatment of osteoclasts with antisense ODN decreased NCX1 protein level.

In conclusion, NCX1 may play a role in the osteoclastic bone resorption and KB-R7943, a new NCX1 inhibitor, may be effective in decreasing bone loss and preventing osteoporosis.

SA149

The Effect of Ibandronate on In Vitro and Ex Vivo Inflammatory Cytokine Production. Anthony R. Lyons,[1] Sharon Crouch,[2] Andrew Wilcock,[3] [1]Orthopaedic and Accident Surgery, University of Nottingham, Nottingham, Notts, United Kingdom, [2]David Evans Research Centre, City Hospital, Nottingham, Notts, United Kingdom, [3]Hayward House, City Hospital, Nottingham, Notts, United Kingdom.

Some patients with cancer and bone metastases report an improvement in pain following the intravenous administration of bisphosphonates, the mechanism for which is unclear. The response cannot as yet be predicted. We have investigated in-vitro the effect of ibandronate - a potent bisphosphonate, on cytokine secretion from mononuclear cells (MNC) isolated from the peripheral blood (PB) of patients with prostate cancer and with widespread bony metastases attending a palliative care clinic. We found significant inhibition ($p<0.01$, $n=10$) with 10ngml-1 of ibandronate on spontaneous tumour necrosis-a (TNF) and interleukin-8 (IL-8). A further 6 patients entered a clinical study and received ibandronate 2mg, 4mg, 6mg or placebo as an intra-venous infusion. Serum was taken prior to infusion and at 90mins and 7 days post-infusion and assayed by ELISA for the presence of TNF, interleukin-1b (IL-1), interleukin-8 (IL-8), interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1ra) and soluble TNF receptor type I (sTNFR). All but TNF and IL-1 were detected. Serum levels of IL-6 and IL-8 correlated with pain severity assessed by a numerical rating scale ($p<0.001$). There was however, no dose dependent effect of ibandronate on circulating cytokine levels or pain scores. MNC isolated from the PB of these patients showed a significant drop in IL-6 levels ($p=0.04$) in unstimulated (no lipopolysaccharide (LPS)) MNC-conditioned media harvested after 18 hours. IL-8 fell in 3/6 patients and remained unchanged in the other subjects but this fall was not statistically significant. The changes seen with IL-6 and IL-8 were not dose related. In the presence of 1ng ml-1 LPS there were non-significant reductions in IL-6 and IL-8 production. The inhibitory effect of ibandronate in vitro and ex vivo on the MNC production of such pro-inflammatory cytokines suggests a possible mechanism by which pain could be improved. The relationship between the severity of pain and serum levels of IL-6 and IL-8 and the effect upon these of intravenous bisphosphonates should be examined in a larger number of patients.

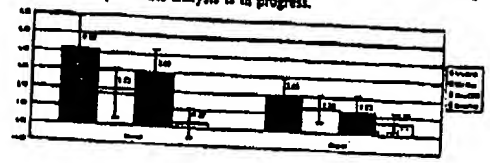
SA150

Osteoprotegerin Increases Femoral Mechanical Properties in Control and Tail Suspended Mice. T. A. Bateman,[1] Colin R. Dunstan,[2] Virginia L. Ferguson,[1] Reed A. Avery,[1] Simuke J. Simske,[1] [1]BioServe Space Technologies, University of Colorado, Boulder, CO, [2]Amgen Inc., Thousand Oaks, CA.

This experiment examined the effect of osteoprotegerin (OPG) on the mechanical properties of the long bones in maturing mice using tail suspension as a formation inhibiting model. A total of 54 male C57 mice were assigned to five groups. A Baseline group (n=10) was sacrificed on day 0 of the study (33 days old). The remaining mice were divided into suspension or vivarium control groups. Half received 0.3mg/kg/day rh Fc OPG (Amgen Inc.) (i.p.), the other half a placebo (n=11/grp). Sacrifice occurred on day 10. After sacrifice the left femora, tibiae and humeri were prepared for mechanical testing (3-point bending to failure) and right limbs for histology. A compositional analysis was performed on the fractured bones. Min-M and Org-M represent the mass of mineral and organic phases, respectively (Dry-M = Min-M + Org-M. %Min = Min-M/Dry-M).

OPG significantly increased femoral elastic strength (13.9%) in control mice and elastic stiffness (20.7%) and maximum strength (8.1%) in suspended mice. Femoral Dry-M was increased for both control (10.5%) and suspended (11.3%) mice. The mineral phase of the bones was affected to a greater degree than the organic matrix, depicted in Figure 1 as an increase in mass from mean mass of the Baseline group (error bars = 1 s.d.). Tibial and humeral Min-M and Org-M were similarly changed. OPG highly significantly increased femoral, tibial and humeral %Min for both control and suspension groups ($p<0.001$ for all comparisons).

The combination of increased bone mass and percent mineralization contributed to the increase in mechanical properties. The mechanism for increasing mineralization and bone mass is unknown and merits further investigation. Quantitative histomorphometric analysis is in progress.



SA151

Hydrophobic Modifications at the Amino-Terminal Cysteine of Recombinant Sonic Hedgehog Signaling Domain Dramatically Increase Activity. Tilman Seyfter,[1] Petra Rueger,[1] Ulrike Leger,[1] Barbara Zehentner,[2] Manfred Wozny,[1] Stefan Koch,[1] Helmut Buttscher,[1] Apollon Papadimitriou,[1] Gabriele Proetzel,[1] Konrad Honold,[1] Friedrich Popp,[1] Peter-Paul Ochlich,[1] Lothar Kline,[1] Carola Dony,[1] Kurt Lang,[1] [1]Roche Diagnostics Boehringer Mannheim GmbH, Penzberg / Mannheim, Germany, [2]Institut für Biotechnologie, Martin-Luther-Universitaet Halle-Wittenberg, Halle, Germany.

Hedgehog (Hh) proteins represent a new family of morphogens which in vertebrates also play a crucial role in skeletogenesis and cardiage formation. The secretory full length Hh precursor protein undergoes an autoprocessing reaction resulting in an amino-terminal signaling domain (Hh-N) which is cholesterol-modified at the carboxy-terminus. We expressed the amino-terminal signaling domain of human Sonic Hedgehog (hShh-N) as a soluble secreted protein in a Baculo virus system. Upon purification of conditioned Baculo virus supernatant by column chromatography under native conditions we were able to isolate a modified form of hShh-N with dramatically increased activity from the majority of the much less active unmodified Hh protein. Analysis by mass spectrometry and peptide mapping revealed that the enhanced activity is due to palmitoylation of the amino-terminal cysteine of hShh-N. A comparison between the activity of purified palmitoylated hShh-N and the activity of unmodified hShh-N purified from *E. coli* resulted in about thousand fold higher specific activity of the hShh-N derivative. This tremendous difference in specific activity was shown both by induction of alkaline phosphatase activity in C3H10T1/2 cells and by quantitative PCR measurements of mRNA levels of ptc and gli which represent two downstream genes of the Shh signaling cascade. *In vitro* acylation of *E. coli* derived hShh-N resulted in an up to thousand fold increase of specific activity depending on the chemical nature and localization of the lipid-modification. Myristoylation or lauroylation of the amino-terminal cysteine for example results in 50% or 10% of the activity of palmitoylated hShh-N respectively whereas multiple random palmitoylation increases activity only to a minor extent. Our data show that amino-terminal palmitoylation of hShh-N happens naturally in eukaryotic cells. An increase in hydrophobicity especially at the amino-terminus of hShh leads to a dramatic enhancement of its activity independent of the presence of the carboxy-terminal cholesterol-modification. The physiological function of the amino-terminal lipid modification of Hh-N is currently under investigation.

PTO/SB/17 (10-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 770.00

Complete If Known	
Application Number	09/844257
Filing Date	April 27, 2001
First Named Inventor	Karin Kellner
Examiner Name	M. T. Brannock
Art Unit	1646
Attorney Docket No.	CIBT-P01-099

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 18-1945

Deposit Account Name: Ropes & Gray LLP

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below	=	Fee Paid
Total Claims		-** =		x		=	
Independent Claims		-** =		x		=	
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	430.00
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	340.00
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 770.00

SUBMITTED BY

				(Complete *(if applicable)*)	
Name (Print/Type)	Melissa S. Rones, Ph.D.	*Registration No. (Attorney/Agent)*	54,408	*Telephone*	(617) 951-7653
Signature				*Date*	November 5, 2004

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 11/5/04 Signature: _____ (Ginny Blundell)

PTO/SB/22 (08-04)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) CIBT-P01-099
Application Number 09/844257	Filed April 27, 2001
For METHODS AND REAGENTS FOR TISSUE ENGINEERING OF CARTILAGE IN VITRO	
Art Unit 1646	Examiner M. T. Brannock

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
[ ]	One month (37 CFR 1.17(a)(1))	$110.00	$55.00	$
[x]	Two months (37 CFR 1.17(a)(2))	$430.00	$215.00	$ 430.00
[ ]	Three months (37 CFR 1.17(a)(3))	$980.00	$490.00	$
[ ]	Four months (37 CFR 1.17(a)(4))	$1,530.00	$765.00	$
[ ]	Five months (37 CFR 1.17(a)(5))	$2,080.00	$1,040.00	$

[ ] Applicant claims small entity status. See 37 CFR 1.27.

[ ] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[x] The Director has already been authorized to charge fees in this application to a Deposit Account.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 18-1945 . I have enclosed a duplicate copy of this sheet.

I am the

[ ] applicant/inventor.

[ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

[x] attorney or agent of record. Registration Number 54,408

[ ] attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) _____

Signature — November 5, 2004 (Date)

Melissa S. Rones, Ph.D. (Typed or printed name) — (617) 951-7653 (Telephone Number)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

[x] Total of 1 forms are submitted.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 11/5/04 Signature: _____ (Ginny Blundell)

PTO/SB/17 (10-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 110.00

Complete if Known	
Application Number	09/844257
Filing Date	April 27, 2001
First Named Inventor	Karin Kellner
Examiner Name	M. T. Brannock
Art Unit	1646
Attorney Docket No.	CIBT-P01-099

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 18-1945

Deposit Account Name: Ropes & Gray LLP

The Director is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims	Fee from below	Fee Paid
Total Claims	-20** =		x =	
Independant Claims	-3** =		x =	
Multiple Dependent			=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	88	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	110.00
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
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Other fee (specify)					

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 110.00

SUBMITTED BY

(Complete *(if applicable)*)

Name (Print/Type)	Melissa S. Rones, Ph.D.	*Registration No. (Attorney/Agent)*	54,408	*Telephone*	(617) 951-7653
Signature				*Date*	October 5, 2004

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Dated: 10/5/04 Signature: _____ (Ginny Blundell)